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Rationale and design of the peripheral nerve tumor registry: an observational cohort study

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ABSTRACT

Aim: Peripheral nerve tumors (PNT) are rare lesions. To date, no systematic multicenter studies on epidemiology, clinical symptoms, treatment strategies and outcomes, genetic and histopathologic features, as well as imaging characteristics of PNT were published. The main goal of our PNT Registry is the systematic multicenter investigation to improve our understanding of PNT and to assist future interventional studies in establishing hypotheses, determining potential endpoints, and assessing treatment efficacy.

Methods: Aims of the PNT registry were set at the 2015 Meeting of the Section of Peripheral Nerve Surgery of the German Society of Neurosurgery. A study protocol was developed by specialists in PNT care. A minimal data set on clinical status, treatment types and outcomes is reported by each participating center at initial contact with the patient and after 1 year, 2 years, and 5 years. Since the study is coordinated by the Charité Berlin, the PNR Registry was approved by the Charité ethics committee (EA4/058/17) and registered with the German Trials Registry (www.drks.de). On a national level, patient inclusion began in June 2016. The registry was rolled out across Europe at the 2019 meeting of the European Association of Neurosurgery in Dublin.

Results: Patient recruitment has been initiated at 10 centers throughout Europe and 14 additional centers are currently applying for local ethics approval.

Conclusion: To date, the PNT registry has grown into an international study group with regular scientific and clinical exchange awaiting the first results of the retrospective study arm.

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Introduction

Peripheral nerve tumors (PNT) are rare lesions most frequently located at extremities, torso, or neck [1–3]. Clinical symptoms frequently involve pain, muscle weakness, or sensory deficits. Tumor size, location, and exact subentity of PNT vary substantially, and there is a large spectrum of therapeutic strategies, outcomes, and prognoses. In the initial phase of treatment, the main choice is between biopsy, surgical resection, or conservative management [4]. To date, clinical trial evidence with robust epidemiological and clinical information is limited mainly to schwannoma and neurofibroma, which are most frequent among PNT and benign in character [1–3]. Single center series with moderate case load report on varying results with respect to epidemiology, outcome, and treatment strategies and lacking unifying reporting standards [5–8]. Rarer entities are only scarcely reported on, such as desmoid, lymphoma, lipoma, amyloidoma, and malignant peripheral nerve sheath tumors (MPNST) [3,9–11].

The main goal of the PNT Registry is to systematically examine the prevalence of PNT, clinical symptoms, treatment strategies and outcomes, genetic and histopathologic features, and imaging characteristics. The PNT Registry seeks to improve our understanding of PNT and to assist future interventional studies in establishing hypotheses, determining potential endpoints, and assessing treatment efficacy.

Methods

The peripheral nerve tumor study group

Initial planning on the PNT Registry began at the 2015 Meeting of the Section of Peripheral Nerve Surgery of the German Society of Neurosurgery, at which the first group of participating centers was established. Since the study is coordinated by the Charité Berlin, the PNR Registry was approved by the Charité's ethics committee (EA4/058/17) and registered with the German Trials Registry (www.drks.de). On a national level, patient inclusion began in June 2016. The registry was rolled out across Europe at the 2019 meeting of the European Association of Neurosurgery in Dublin. To date, numerous centers throughout Europe have either already started including cases or have expressed interest in participating. Prior to participation, each center has to establish approval by its local ethics committee.

Aims, patient eligibility, and data flow

A steering committee was appointed in 2015 that defined the aims of the PNT Registry. These are:

- to document which types of treatments are being conducted
- to monitor the natural history in patients with conservative management, and outcomes in patients undergoing specific interventions
- to collect imaging data both before treatment and during follow-up (at 1, 2, and 5 years)
- to continue inviting additional centers both interdisciplinarily (including oncology and neurology) and internationally.

The following inclusion criteria were established:

- diagnosis of a tumor associated with a peripheral nerve on MRI, CT, or sonogram
- informed consent

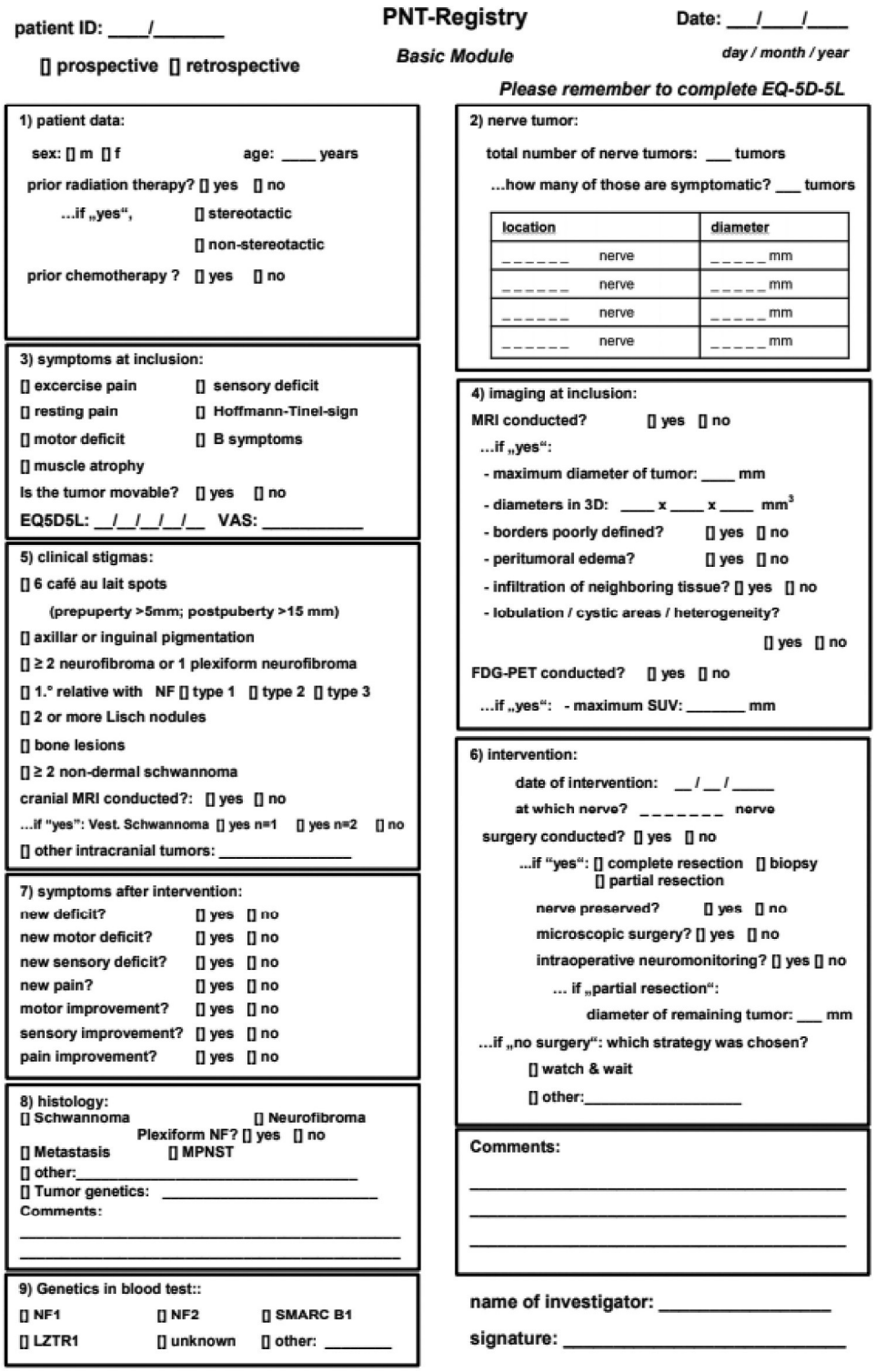
There are no exclusion criteria. If patients are unable to give informed consent due to their clinical status, or if the patient is under 18 years, informed consent is requested from the legal representative of the patient. For underaged patients, age-appropriate information material is available for groups aged 6–12 years and 13–17 years.

Data flow will be managed by each participating center itself. Patient recruitment is consecutive. There is a prospective and a retrospective part of the PNR Registry. In the retrospective part, patients can be included back to the year 2015, depending on initial presentation to the participating center. Data collection takes place at initial hospital admission or outpatient contact and at follow-up visits at 1, 2, and 5 years after inclusion. Patients receive a pseudonymized ID for inclusion into the registry.

Study protocol

A study protocol was designed by the steering committee. In this process, potentially valuable variables were discussed based on current evidence on PNT. The main focus was on selecting variables that can be assessed at centers of all sizes even in a setup of minimal technical capability.

Data collection at initial contact is conducted using a Basic Case Report Form (B-CRF), as shown in Figure 1. This B-CRF was designed to address a manageable amount of variables to ensure safe and uncomplicated documentation. It gathers demographic and clinical data between first contact and discharge after treatment initiation at the participating center. A neurological examination is conducted and results are reported according to reliable and established grading systems. The type of treatment is recorded with conservative and surgical options. Potential complications can also be documented. Follow-up study visits are reported on separate follow-up CRFs (F-CRF) with a minimal amount of additional variables.


patient ID: ____/_____

[] prospective [] retrospective

PNT-Registry

Basic Module

Date: ___/____/____

day / month / year

Please remember to complete EQ-5D-5L

1) patient data:

sex: [] m [] f age: ____ years

prior radiation therapy? [] yes [] no

...if „yes“, [] stereotactic

[] non-stereotactic

prior chemotherapy ? [] yes [] no

2) nerve tumor:

total number of nerve tumors: ___ tumors

...how many of those are symptomatic? ___ tumors

location	diameter
_____ nerve	_____ mm
_____ nerve	_____ mm
_____ nerve	_____ mm
_____ nerve	_____ mm

3) symptoms at inclusion:

[] excercise pain [] sensory deficit

[] resting pain [] Hoffmann-Tinel-sign

[] motor deficit [] B symptoms

[] muscle atrophy

Is the tumor movable? [] yes [] no

EQ5D5L: __/__/__/__/__ VAS: _____

4) imaging at inclusion:

MRI conducted? [] yes [] no

...if „yes“:

- maximum diameter of tumor: ____ mm
- diameters in 3D: ____ x ____ x ____ mm^3
- borders poorly defined? [] yes [] no
- peritumoral edema? [] yes [] no
- infiltration of neighboring tissue? [] yes [] no
- lobulation / cystic areas / heterogeneity? [] yes [] no

FDG-PET conducted? [] yes [] no

...if „yes“: - maximum SUV: _____ mm

5) clinical stigmas:

[] 6 café au lait spots

(prepuperty >5mm; postpuberty >15 mm)

[] axillar or inguinal pigmentation

[] ≥ 2 neurofibroma or 1 plexiform neurofibroma

[] 1.° relative with NF [] type 1 [] type 2 [] type 3

[] 2 or more Lisch nodules

[] bone lesions

[] ≥ 2 non-dermal schwannoma

cranial MRI conducted?: [] yes [] no

...if "yes": Vest. Schwannoma [] yes n=1 [] yes n=2 [] no

[] other intracranial tumors: _____

6) intervention:

date of intervention: __/__/____

at which nerve? _____ nerve

surgery conducted? [] yes [] no

...if "yes": [] complete resection [] biopsy [] partial resection

nerve preserved? [] yes [] no

microscopic surgery? [] yes [] no

intraoperative neuromonitoring? [] yes [] no

... if „partial resection“:

diameter of remaining tumor: ___ mm

...if „no surgery“: which strategy was chosen?

[] watch & wait

[] other:_____

7) symptoms after intervention:

new deficit? [] yes [] no

new motor deficit? [] yes [] no

new sensory deficit? [] yes [] no

new pain? [] yes [] no

motor improvement? [] yes [] no

sensory improvement? [] yes [] no

pain improvement? [] yes [] no

Comments:

_____

_____

_____

8) histology:

[] Schwannoma [] Neurofibroma

Plexiform NF? [] yes [] no

[] Metastasis [] MPNST

[] other:_____

[] Tumor genetics: _____

Comments:

_____

_____

9) Genetics in blood test::

[] NF1 [] NF2 [] SMARC B1

[] LZTR1 [] unknown [] other: _____

name of investigator: _____

signature: _____

Figure 1. Baseline CRF. This CRF is completed by each center at initial patient inclusion. FU, follow-up; MRI, magnetic resonance imaging; FDG-PET, fluorodeoxyglucose positrone emission tomography; SUV, standardized uptake value; MPNST, malignant peripheral nerve sheath tumor; NF, neurofibroma; SMARCB1, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1; LZTR 1, Leucine-zipper-like transcriptional regulator 1.

Study endpoints, patient risk, and statistical analyses

The following primary endpoints were defined

1) functional outcome at 1 year regarding motor and sensory function, pain, and quality of life,

2) tumor size at 1 year or diagnosis of tumor recurrence.

Since the registry is a non-interventional, purely observational study, and treatment strategies are devised by specialists at each center independent of the registry, there is no added risk for participating patients. Statistical analyses are conducted by the Institute of Biometry and Clinical Epidemiology at the Charité Berlin. Since the registry does not aim to

examine a specific hypothesis, there is no set case number as a goal. Depending on center volume, 5–50 annual PNT cases are expected per center. The analysis will be descriptive in nature to allow for a formulation of hypotheses in future studies. Statistical methods will include event history analyses and binary regression analyses with the endpoints as dependent variables and factors such as patient age, sex, tumor size and complete tumor resection as independent variables. A report of the first results is planned after the first 100 patients will be included retrospectively and prospectively.

Data protection measures

The data protection concept of the registry was approved by the Department for Data Protection at the Charité Berlin. Patients will be included using a pseudonymized ID that allows for de-pseudonymization only by the center that included the case. Each center has the option to either send the filled in CRF with the pseudonymized data by email or directly add data to a password protected online data base data that can be accessed by the coordinating center for analyses.

Patient recruitment

Patient recruitment has begun at 10 centers throughout Europe and 14 additional centers are currently applying for local ethics approval.

Summary and conclusion

Since PNT are rare lesions, scientific evidence on these lesions is scarce and no specific treatment standards have been defined. Patients with PNT are therefore treated based on individual experience of the local specialist rather than on standardized guidelines. The need for systematic evidence from all disciplines involved in PNT management is the main driver for the establishment of the PNT Registry. This study is unique in that it is the first international prospective registry exclusively focused on PNT. Based on a study protocol developed by specialists in PNT care, a minimal data set on clinical status, treatment types, and outcomes is reported by each participating center at initial contact with the patient and after 1 year, 2 years, and 5 years. The registry aims to inform future interventional studies on PNT. The main limitation of the registry is its purely observational, non-interventional character, which does not allow for comparisons to control groups. Also, since the registry does not require the adherence to certain treatment types and centers are free to devise treatment strategies independent of the registry, our study does not allow for thorough understanding of the rationale underlying each treatment. Nevertheless, since there are no guidelines on PNT management, these limitations are not more pronounced than in routine clinical practice. To date, the PNT registry has grown into an international study group with regular scientific and clinical exchange.

Authors contributor

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Notes on contributor

Nora F. Dengler is a senior physician at the Department of Neurosurgery at Charité Berlin. She has special interests in peripheral nerve, spine, vascular and skull base surgery. She currently serves as chair in the section of peripheral nerve surgery of the German Neurosurgical Society (DGNC) and is board member and comitee member of the peripheral nerve surgery sections of the European Association of Neurosurgical Societies (EANS) and the World Federation of Neurosurgical Societies (WFNS).

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